

REMARKS

Claims 1-20 are pending. Claims 1 and 7 are rejected. Claims 14-20 are withdrawn and by this Amendment are canceled without prejudice.

CLAIM REJECTIONS UNDER 35 U.S.C. §112

Claims 1 and 7 are rejected under 35 U.S.C. §112 ¶ 1 as not described new matter. The Examiner states "The specification as originally filed does not specifically teach the concept that *each* polar head group having a straight-chained hydrophobic group has a different chain length from an adjacent hydrophobic group" (emphasis in original).

Applicants have amended claims 1 and 7 to overcome the rejection. While each polar head group need not have a different chain length from an adjacent group, chain lengths must be sufficiently different for longer chains to assemble beneath adjacent shorter chains to enhance rigidity of the shell. The amended claims recite these limitations. Applicants thus believe the rejection is overcome and requests its withdrawal.

CLAIM REJECTIONS UNDER 35 U.S.C. §102

Claims 1 and 7 are rejected under 35 U.S.C. §102(b) as anticipated by Unger. Applicants disagree.

Unger's lipid "combinations thereof" do not disclose a selection of lipids whereby straight-chain hydrophobic groups have different chain lengths sufficient for longer chains to assemble beneath adjacent shorter chains to enhance rigidity of the shell. Unger's composition would not inherently result in Applicants' assembly, at least because Unger does not disclose these lipid combinations as selected to be positioned so that assembly results in the desired enhanced rigidity of the composition.

Applicants further dispute (1) the Examiner's interpretation of Unger's self-assembly resulting in Applicant's composition, and (2) that Applicants' specification supports the Examiner's interpretation. A "mixture or blend of fatty acids which may have different carbon chain lengths" would not contain the proper chain lengths unless selected to do so. In support, Applicants point to their FIG. 1, requiring specific lipids of differing chain lengths, namely, sodium triacontanoate, sodium docosanoate, and docosamidePEG[120]. Applicants' straight chain hydrophobic groups are selected for their properties.

Claims 1 and 7 are rejected under 35 U.S.C. §102(b) as anticipated by Klaveness. Applicants disagree.

Applicants incorporate their distinctions set forth with respect to Unger.

Klaveness, in the section the Examiner applied, categorizes his amphiphiles into the following three categories: (1) carrying at least two simple reactive groups capable of reacting with polyvalent reactive monomers or preformed polymers; (2) polymerizable groups that can be caused to polymerize after vesicle formation; or (3) soluble amphiphilic polymers carrying

appropriate functional groups that may be further polymerized or crosslinked after vesicle formation. None of the disclosure for any of these groups relate to the length of the straight-chained hydrophobic group selected as having different chain lengths sufficient for longer chains to assemble beneath adjacent shorter chains thereby enhancing rigidity of the shell. Because Applicants claim these embodiments, and because Klaveness does not disclose these embodiments, Klaveness does not anticipate.

The Examiner states

It is interpreted that when a mixture or blend of fatty acids which may have different carbon chain lengths are employed in the preparation of microbubbles, the microbubble would inherently be organized via self assembly such that a hydrophobic group with a given chain length would be adjacent to another hydrophobic group with a different chain length.

Applicants disagree. As analyzed above, Klaveness' composition would not contain the proper chain lengths to achieve Applicants' "molecular corrugation" unless selected to do so. Applicants' straight chain hydrophobic groups are selected for their properties.

Claims 1 and 7 are rejected under 35 U.S.C. §102(b) as anticipated by Rasor.

The Examiner states that Rasor's "fatty acid is myristic, palmitic, stearic, arachic acid or a *mixture thereof*" (emphasis in original).

Applicants dispute that "a mixture thereof" is identical to, and thus anticipates, their selection of lipids whereby straight-chain hydrophobic groups have different chain lengths sufficient for longer chains to assemble beneath adjacent shorter chains to enhance rigidity of the shell. Rasor's composition would not inherently result in Applicants' assembly at least because Rasor does not disclose these lipid combinations as selected to be positioned so that assembly occurs resulting in the desired enhanced rigidity of the composition.

Claims 1 and 7 are rejected under 35 U.S.C. §102(e) as anticipated by Church.

The Examiner states "Lipids which may be used to stabilize gas inside the microparticles include fatty acids, phospholipids, etc., including mixture of fatty acids between 6 and 24 carbon atoms."

Church's recitation of various such lipids and his mixtures of fatty acids do not disclose a selection of lipids whereby straight-chain hydrophobic groups have different chain lengths sufficient for longer chains to assemble beneath adjacent shorter chains to enhance rigidity of the shell.

Applicants also dispute the Examiner's interpretation "that when a mixture of fatty acids are employed which may have different carbon chain lengths, the microbubble would inherently be organized via self assembly such that a hydrophobic group with a given chain length would be adjacent to another hydrophobic group with a different chain length." Church's composition would not inherently result in Applicants' assembly at least because Church does not disclose these lipid combinations as selected to be positioned so that assembly occurs resulting in the desired enhanced rigidity of the composition.

In view of Applicants' amendments and arguments set forth above, Applicants assert that none of Unger, Klaveness, Rasor, or Church anticipate claims 1 and 7, and request the 35 U.S.C. §102 rejections be withdrawn.

CLAIM REJECTIONS UNDER 35 U.S.C. §103

Claims 1-13 are rejected under 35 U.S.C. §103(a) as obvious over either Unger or Klaveness. The Examiner states

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use a combination (or blend or mixture) of any encompassed by the claimed formula because both Unger and Klaveness teach that such shell materials in a microbubble for a stable, safe, and effective ultrasound contrast agent to improve methods of ultrasound imaging [*sic*].

Regarding Unger, incorporating the previous arguments distinguishing it, Unger's

[[The]] gaseous precursor-filled liposomes also have the advantages, for example, of stable particle size, low toxicity and compliant membranes. It is believed that the flexible membranes of the gaseous precursor-filled liposomes may be useful in aiding the accumulation or targeting of these liposomes to tissues such as tumors (col. 4 lines 28-34, emphasis added).

Thus, Unger specifically seeks membranes that are "compliant" and "flexible". Applicants, in contrast, claim microbubbles with "enhanced rigidity" of the shells. Unger therefore teaches away from Applicants' composition and, as such, is not obvious for at least this reason.

Regarding Klaveness, he achieves stability by crosslinking polymers.

...polymers containing chemically linked surface active, i.e., amphiphilic, moieties. Thus the surface active properties of the amphiphilic groups stabilize the microbubble system by reducing surface tension at the gas-liquid interface...while the linking of the groups through the polymer system generates further stability (col. 1 lines 54-60).

However, Klaveness seeks both flexibility and stability and achieves this by crosslinking shell polymers. "Flexibility of the encapsulating materials also enhances the image density afforded by such contrast agents" (col. 1 lines 60-62). Thus, Applicants previous arguments above distinguishing flexible shells from their rigid shells apply here with respect to Klaveness.

In view of Applicants' amendments and arguments set forth above, Applicants assert that neither Unger nor Klaveness render claims 1-13 obvious, and request the 35 U.S.C. §103 rejections be withdrawn.

CONCLUSION

Applicants authorize credit card payment of a two-month extension for response (see electronic fee sheet). Applicants do not believe any other fees are due but, if necessary, the Examiner is authorized to charge them (or credit any overpayment) to Deposit Account No. 23-3000.

The Examiner is invited to contact Applicants' undersigned representative with questions.

Respectfully submitted,

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